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TRINITROTOLUENE POISONING.[1]

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Results of Experimental Study of Trinitrotoluene Poisoning.

The following conclusions were reached from an extensive study of chromic T. N. T. poisoning in dogs. The investigation was, later on, extended by work in a large shell-filling plant.

1. *Species susceptibility.*—Different species of animals (including man) exhibit considerable differences in their resistance to the toxic action of T. N. T. Dogs and cats (probably also men) are far more susceptible than white rats, guinea pigs, and rabbits. For this reason dogs were selected for this work.

2. *Symptoms.*—Cyanosis, constipation followed by diarrhea, salivation, incoordination, icterus, and anæmia were observed. The clinical picture very often changes during the course of poisoning. For instance, cyanosis, which is almost always present at the beginning of the intoxication, may disappear later on. A considerable loss of body weight was observed in some of the animals; in others there was a preliminary loss followed by recovery; in a few no change was noted until shortly before death.

3. *Absorption.*—T. N. T. is readily absorbed when administered subcutaneously, dissolved in oil, when given by mouth in gelatin capsules, and finally, when introduced as dust into the lower air passages. The blood plasma of animals receiving T. N. T. often yields a positive Webster test.

4. *Excretion.*—The urine of animals gives a positive Webster test within two or three hours following the administration of T. N. T. The color of the urine assumes a red appearance, the red disappearing on the addition of acid. This red color is quite characteristic of urine in the early stages of the intoxication. The substance which is responsible for the urinary Webster test is not T. N. T., but a metabolism product of the latter. In some cases bile removed at necropsy yields a positive Webster test, indicating that T. N. T. or some of its derivatives are excreted with the bile. The feces never give a positive Webster test. It is important to note that whereas the urinary Webster reaction is very intense at the beginning of the poisoning, the test is very often negative in the later stages. This observation seems to indicate that the animal body in some unknown way changes its method of dealing with this poison.

5. *Doses used.*—T. N. T. was given to dogs daily (excluding Sundays) over long periods and in doses of 5 to 33 milligrams per kilo body weight. The minimum toxic dose has not been determined,

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[1] From a paper read at the annual meeting of the American Federation of Biological Societies in Baltimore, Md., April 24, 1919.

but it should be definitely stated that it is less than 5 milligrams per kilo (probably less than 180 milligrams for an adult man).

6. *Individual susceptibility.*—A striking feature of T. N. T. poisoning in dogs is the great difference in individual susceptibility to poisoning. An animal receiving 10 milligrams per kilo may show more severe symptoms than other animals receiving 30 milligrams per kilo. It is unlikely that this variation in individual susceptibility is due to differences in absorption. It was furthermore observed that animals with a slight grade of anæmia or of some infection are more susceptible to T. N. T. poisoning.

7. *Tolerance.*—Dogs receiving T. N. T. do not acquire a tolerance to this poison in the sense that they become immune to the toxic action of T. N. T. It was found, however, that, as a rule, the clinical symptoms are much more pronounced after the first few doses than later on. Thus the cyanosis and incoordination may disappear completely in the later stages of poisoning.

8. *Impurities.*—No qualitative or quantitative difference was observed in the toxic action of crude or highly purified T. N. T. The toxicity of the commercial product is due to trinitrotoluene per se and is not increased by the presence of small amounts of impurities.

9. *Prophylactic value of diet.*—Dogs fed on a meat diet are more resistant to T. N. T. poisoning than dogs which are fed white bread and milk. Meat has, therefore, greater prophylactic power than milk, as far as dogs are concerned.

10. *Anæmia and toxic jaundice.*—Every animal subjected to chronic T. N. T. poisoning has developed an anæmia of varying intensity. The following blood changes were observed: A reduction in the total blood volume, the red corpuscle volume, the hemoglobin and the pigment volume; the appearance of nucleated red blood cells and an increase in reticulated blood cells. Anisocytosis is very common, especially during the first few weeks of poisoning. Finally, the number of red blood cells shows a very considerable decrease. It should be emphasized, however, that certain animals may show a normal red-blood cell count at a time when other blood tests give evidence of the presence of a severe degree of anæmia.

Among the urinary changes observed should be mentioned the appearance of bile pigments. A considerable number of animals never show bile pigments in the urine. On the other hand, animals which develop jaundice always give a positive test for bile pigments during the period preceding the appearance of clinical signs of jaundice. Urine from T. N. T. dogs never contains more than traces of albumin, and the Fehling test is only slightly positive at times. No significance should be attached to these findings, as normal dog urine occasionally gives a faint test for protein and sugar.

11. *Necropsy findings.*—The gross pathological findings at necropsy are as follows: Decrease of muscular tissue, degeneration of liver, splenic tumor or decrease in size of spleen, occasionally general jaundice. The bone marrow has very often a hyperplastic appearance, while in other instances a fatty marrow is found.

12. *Experimental work on prevention of skin absorption.*[1]—After considerable experimentation, a skin varnish was developed which appears to possess all the desirable features. The varnish is composed of 6 parts of shellac, 1 part of castor oil, and 24 parts of 95 per cent alcohol. This varnish when applied to the hands and forearms dries very easily. The brown film which is thus formed is flexible and does not peel off. It is resistant to perspiration and moisture. In other words, it has all the desirable physical properties of a protective varnish. Experiments made on rabbits and on the human skin with this varnish have demonstrated that the intense local irritation caused by the local application of "parazol" can be avoided. It is reasonable to assume that in a similar way skin absorption of T. N. T. could be prevented. The varnish is very easily removed from the skin by means of alcohol.

Another method of skin protection has been worked out by changing the composition of the above varnish for the purpose of producing an impermeable glove. Cotton gloves treated with a varnish of the following composition: Two parts shellac, 1 part castor oil, and 8 parts of alcohol, appear to be very satisfactory for use by T. N. T. workers. The texture of the glove remains fairly flexible, the varnish does not crack and is resistant and impermeable to water.

At the suggestion of Dr. Alice Hamilton, a number of T. N. T. solvents were tested as to their efficiency as a wash for T. N. T. workers. It was found that a 10 per cent solution of sodium hydrosulphite is the best inorganic solvent known at the present time. The next best solvent is sodium sulphite. The solubilities of T. N. T. in these solvents at room temperature are as follows: 100 cc. 10 per cent. sodium hydrosulphite dissolves 0.128 gram of T. N. T. 100 cc. of 10 per cent sodium sulphite dissolves 0.082 gram of T. N. T.

Diagnosis and Measures of Protection and Precaution.

1. *Diagnostic tests for recognition of early poisoning.*—Anæmia is a constant and early sign of T. N. T. poisoning in animals. It is, therefore, recommended that an accurate hemoglobin estimation be made on all new workers entering a factory where T. N. T. is either manufactured or used for the production of munitions. As a reliable instrument for this purpose we recommend the Sahli hemoglobinometer. The blood of the workers should be tested by means

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[1] The work on the protective varnish was carried out by Dr. George F. White under the direction of the senior author of this paper.

of this instrument every 8 to 14 days and workers showing a decrease of 15 to 20 per cent in the hemoglobin below the initial figure should be taken off T. N. T. work.

Work which was carried out in a large shell-filling plant has demonstrated the value of the hemoglobin determination for the recognition of mild poisoning.

Another test which should be made every 8 to 14 days is the examination of the urine for bile pigments. A positive test is sufficient reason to take a worker off T. N. T., as the appearance of bile pigments indicates a serious disturbance in the normal liver function, which may rapidly lead to toxic jaundice. For the bile pigment test we recommend the Huppert test or, when sufficient time is not available, Rosenbach's modification of Gmelin's test. In addition to these tests careful attention ought to be given to the presence of clinical symptoms, such as cyanosis and possibly slight incoordination. This last symptom hitherto has not been described for T. N. T. poisoning in man, but careful examination might reveal its presence in this condition.

2. *Meat and a generous diet.*—The dietary used by T. N. T. workers should be carefully supervised, as the experimental work has shown that the individual resistance to T. N. T. poisoning is dependent, at least to some extent, on the character of the diet. It is suggested that T. N. T. workers eat at least 150 to 200 grams of meat daily, besides other nourishing foods.

3. *Elimination of susceptible workers.*—The workers showing abnormal susceptibility should be eliminated. According to the report of the British Medical Research Committee, the abnormal susceptibility of certain workers is entirely due to their abnormally permeable skin. The present investigation has shown that there is a considerable variation in individual susceptibility, which is very probably not due to difference in absorption. However this may be, both views warrant the above-mentioned recommendation.

4. *Skin protection.*—In regard to the relative importance of the absorption of T. N. T. (1) through the skin and (2) the respiratory tract, the work done by Prof. E. B. Phelps and Sanitary Chemist E. J. Casselman has shown that the conclusion reached by the British investigators, namely, that skin absorption is the principal factor in the production of T. N. T. poisoning in the human, is correct. However, analyses in certain parts of the factory have demonstrated the presence of considerable amounts of T. N. T., a fact which should caution against neglecting proper ventilation of the plants.

As a protection against skin absorption of T. N. T. the use of the shellac-castor oil varnish is recommended, either as a skin varnish or for the purpose of the preparation of inexpensive impermeable cotton gloves. The varnish is made up according to the following directions: 6 parts of orange shellac are dissolved in 24 parts of warm 95 per cent alcohol. To the resulting solution 1 part of castor oil is added. The varnish is kept in well stoppered bottles to prevent evaporation of the alcohol.

In addition to the use of the varnish or the impregnated cotton gloves, the workers should be made to wash their hands and forearms with a 10 per cent solution of sodium sulphite before leaving the factory.

A trial of the sulphite wash in a shell-filling plant has demonstrated that the workers are very anxious to use this prophylactic. Chemical analysis has shown that a considerable amount of T. N. T. can be removed from the human skin by this solvent, even after the skin has been thoroughly washed with soap and water.

5. *Exclusion of anæmic workers.*—Workers who show a slight grade of anæmia or any other symptoms which would indicate a lowered body resistance, should be rigidly excluded from contact with T. N. T.

The authors acknowledge excellent assistance rendered in this investigation by Drs. White and Mendenhall, Misses Crane, Connell, and Wright.

The detailed report will appear in the near future as a Hygienic Laboratory Bulletin.

MEDICAL SOCIAL SERVICE FOR NURSES.

The rapid extension of clinic service in connection with the control of venereal diseases, and the recognized importance of skilled follow-up work from every clinic, have led to the preparation of a special course in medical social service for graduate nurses.

This course has been arranged by the Public Health Service, in cooperation with Columbia University, Bellevue Hospital, and the New York School of Social Work. Provision for 15 scholarships has been made by the American Red Cross.

The course opens on July 1 and will continue for approximately four months. Its aim is to offer to qualified women who have had the scientific training of graduate nurse a view of the social problems implied in the control of venereal diseases. Already health departments have asked that at the completion of this course the graduate nurse be assigned to the departments for duty.

At Columbia University the course will be offered in connection with the summer's session at Teachers College, department of nursing and health. Since there is not in existence a group of teachers whose special field is this—the social backgrounds of venereal diseases—the speakers will be drawn from the ranks of those who have